Researchers identify natural tumor suppressor

September 9 2008

Researchers from the University of Pennsylvania School of Medicine have identified a key step in the formation – and suppression – of esophageal cancers and perhaps carcinomas of the breast, head, and neck. By studying human tissue samples, they found that Fbx4, a naturally occurring enzyme, plays a key role in stopping production of another protein called Cyclin D1, which is thought to contribute to the early stages of cancer development.

When mutations block production of Fbx4, Cyclin D1 is not broken down, and subsequently contributes to cancer's advance. Fbx4 acts like a bouncer, stopping trouble before it starts by breaking down Cyclin D1 before it can affect the body.

"Cyclin D1 was identified nearly 20 years ago and after that, it became apparent that it was overexpressed in a high percentage of tumors," says J. Alan Diehl, PhD, Associate Professor of Cancer Biology at the University of Pennsylvania's Abramson Family Cancer Research Institute. "But its expression didn't correlate to mutations within Cyclin D1, so we were looking for a protein that regulates accumulation. That's Fbx4."

For this study, researchers screened 116 esophageal tumors and found 16 mutations. Their findings were published in a recent issue of *Cancer Cell*.

The actual mutations researchers found are located within a highly

conserved region of Fbx4 that functions like an on switch. Mutations within that switch region inhibit activation of Fbx4, which means it can't trigger destruction of Cyclin D1.

The results are important in that they show how Cyclin D1 becomes so prevalent in tumors. Before, it was thought that Cyclin D1 was present because of a mutation somewhere in the DNA of a cell. Instead, this study shows that Cyclin D1 naturally occurs, but our bodies have created a natural defense mechanism that breaks it down before cancer develops.

"When Fbx4 is inactivated, it permits the accumulation of its target, CyclinD1," says Diehl.

While it remains important to define the cause of the initial mutations, this study provides researchers with a better understanding of the early stages of cancer which is crucial to finding a way to reverse the process.

Source: University of Pennsylvania